PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4 -32465A	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/04217	International filing date *(day/month/year)* 23.04.2003	Priority date *(day/month/year)* 24.04.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/05, A61K31/05		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.11.2003	03.06.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Peris Antoli, B Telephone No. +49 89 2399-8476

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/04217

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-5 as originally filed

Claims, Numbers

1-4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-4 (partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-4 (partially)
see separate sheet

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,2,4
	No:	Claims	3
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-4
Industrial applicability (IA)	Yes:	Claims	2,3
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. As indicated in the international search report, the search has been limited to the compounds specified in p. 1, § 3 of the description (namely: 2,6-di-tert-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol and its aldehyde analog) and the general idea underlying the functional definition of compound given in the claims.

1.1 According to Rule 66.1(e) PCT, no international preliminary examination will be carried out in respect of the subject matter which is not covered by the search report. This report on present claims 1-4 is therefore incomplete.

2. For the purpose of this report claims 1-4 have been read as if the $GABA_B$ receptor modulators mentioned therein were restricted to 2,6-di-tert-butyl-4- (3-hydroxy-2, 2-dimethyl-propyl)-phenol and its aldehyde analog.

3. Claims 1 and 4 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

4. Reference is made to the following documents:

D1: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; November 2001 (2001-11) URWYLER STEPHAN ET AL: 'Positive allosteric modulation of native and recombinant gamma-aminobutyric acid B receptors by 2,6-di-tert-butyl-4-(3-hydroxy- 2,2-dimethyl-propyl)-phenol (CGP7930) and its aldehyde analog CGP13501.' Database accession no. PREV200100556739 XP002245722 cited in the application & MOLECULAR PHARMACOLOGY, vol. 60, no. 5, November 2001 (2001-11), pages 963-971, ISSN: 0026-895X

D2: US-A-6 117 908 (2000-09-12)

D3: WO-A-01 41748 (2001-06-14)

D4: WO-A-01 90141 (2001-11-29)

NOVELTY

5. Claim 3 does not meet the requirements of Art. 33(2) PCT because its subject matter is not new over D1 (see below).

5.1 **D1** (abstract) discloses the positive allosteric modulation of GABA-B receptors by 2,6-di-tert-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol (CGP7930) and its aldehyde analog CGP13501. D1 also indicates the potential therapeutic use of said GABA-B modulators.

5.2 Thus, D1 implicitly teaches the use of the aforementioned GABA-B modulators for the preparation of pharmaceutical compositions. D1 hence destroys the novelty of the subject matter of present claim 3.
[Note that a product is only defined by its components and not by its intended use].

6. Claims 1, 2 and 4 meet the requirements of Art. 33(2) PCT because none of the prior art documents cited in the search report discloses the use of positive allosteric modulators of GABA-B receptors for the treatment of the gastrointestinal disorders mentioned in the present claims.

INVENTIVE STEP

7. Claims 1-4 do not meet the requirements of Art. 33(3) PCT for the reasons set out below.

7.1 The principle underlying the subject matter of the present claims 1-4 is the use of positive allosteric modulation of GABA-B receptors for the treatment of certain gastrointestinal disorders, namely: GERD (gastro-esophageal reflux disease), regurgitation, IBS (irritable bowel syndrome), dyspepsia, postoperative complaints and conditions associated with visceral discomfort/pain.

7.2 From the prior art, it is known that activation of GABA-B receptors is associated with the management of certain diseases including, among others, GERD, transient lower esophageal sphincter relaxation (TLESR) and other gastrointestinal disorders. It is also known that GABA-B receptor agonists and allosteric modulators of said receptors can be used in the treatment diseases associated to GABA-B receptor activation. With this respect see e.g.

D2 (claims 1-4 in conjunction) which teaches the use of GABA-B receptor agonists, e.g. baclofen, for the treatment of gastro esophageal reflux disease and/or for treatment of regurgitation in infants;

D3 (claim 3, in conjunction with p. 13, §4 and p. 3, §, 4) which acknowledges the known use of GABA-B receptor agonists (e.g. baclofen) and GABA-B receptor modulators (e.g. CGP7930 -which is a positive allosteric modulator of GABA-B receptor [see point 4.1 above]-) for the treatment of altered gastrointestinal motility, sensitivity and/or secretion disorders, including, among others, heartburn (i.e. esophageal reflux), postoperative ileus, abdominal pain and discomfort, regurgitation, GERD, IBS, dyspepsia; or

D4 (p. 2, l.3-8 and p. 7, l. 22-31) which indicates the potential therapeutic use of GABA-B receptor agonists and allosteric modulators of agonists in the treatment/prevention of the afflictions attributed to GABA-B receptor function or lack thereof, including gastro esophageal reflux.

7.3 In view of the aforementioned teachings, in particular in view of D3 and/or D4, it would have been obvious to the skilled in the art to use known positive allosteric modulators of GABA-B receptors, as is the case of those disclosed in D1, for treating the gastrointestinal diseases specified in present claims 1-4. Thus, **no inventive step** can be recognised for the subject matter of **present claims 1-4.**

INDUSTRIAL APPLICABILITY

8. Claims 2 and 3 satisfy the criterion set forth in Art. 33(4) PCT because their subject matter is susceptible of industrial application.

9. For the assessment of the present claims 1 and 4 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.